PRODIET
MEDICAL NUTRITION

Prodiet Journal

Alzheimer's Disease Edition

Background

Dementia is a comprehensive term for several diseases affecting memory or other cognitive and behavioral skills that significantly interfere with a **person's ability to perform daily activities.**

Its prevalence increases exponentially with aging, doubling every 5.5 years. In Latin America, the prevalence goes from 1.3% at age 60 to 63.9% after age 90[1,2]. Although age is the most well-known risk factor for dementia, it is not a normal part of aging. In addition, dementia does not exclusively affect older people, with cases such as the early onset dementia (defined as the onset of symptoms before age 65), which represents up to 9% of cases[3]. Currently, the number of people living with dementia in the world is approximately 50 million, with the prospect of reaching 152 million in 2050[4]. In Brazil, 55 thousand new cases of dementia are estimated every year[5].

One of the causes of dementia is the Alzheimer's disease (AD), which accounts for 60% to 80% of the cases[6]. There are two forms of AD, sporadic (usually of late onset, after age 65) and familial (usually of early onset, before age 65), which represents 5% of AD cases[7,8]. The most common form of AD is the amnestic impairment, which affects recent memory and the ability to learn new facts. There may be non-amnestic impairment related to language (remembering words), executive functions (affecting reasoning, judgment and problem solving), and visual-spatial function (loss of the ability to identify objects or people, disturbance in the sense of sight and reading)[9,10].

AD can have different stages: mild, moderate, and severe, depending on the progress of the disease and the impairment of cognitive ability and daily activities[11]. The clinical manifestations of dementia in AD go through a stage called mild cognitive impairment (MCI) and the preclinical phase[10,12]. Patients in the MCI stage do not necessarily progress to dementia; however, the risks for this population increase substantially compared to the population without MCI, reaching a conversion rate for dementia of 10% per year[13, 14].

Pathophysiology of AD

Before the MCI phase, AD enters the preclinical phase, which can take years, even decades, before the clinical diagnosis of dementia[10,12,15]. The onset of AD seem to occur in a cascade of events, with mutations in the genes of enzymes that cleave a neuronal transmembrane protein, the amyloid precursor protein (APP), leading to extracellular production and deposition of ß-amyloid peptides. These peptides become neurotoxic through structural reorganization, forming oligomers that aggregate and form senile plaques, differently from what would happen under normal conditions, in which APP cleavage would generate protein fragments that would protect the neuronal metabolism[16]. ß-amyloid peptides and their oligomers change the structure and the synaptic transmission[17] and can **quickly block the mechanism of new memory formation, changing synaptic plasticity**[18].

Another protein, called tau protein, is also involved in AD pathological changes. This protein, which supports the neuronal cytoskeleton, is normally soluble, but in AD cases it becomes hyperphosphorylated and transforms into an insoluble filamentous polymer. This process destabilizes the microtubules, protein structures that are part of the cytoskeleton, leading to their degradation and, consequently, to the death of neurons. This happens because these microtubules transport nutrients and information on neuronal extensions to their cell body and vice versa[20, 21]. As a result of tau protein hyperphosphorylation, the anatomical pathology of AD identifies intraneuronal neurofibrillary tangles[21] that impair axonal transport, resulting in synaptic function deficit and neuronal death[22].

Thus, the deposition of ß-amyloid in senile plaques and the tau protein accumulated in neurofibrillary tangles define AD as a unique neurodegenerative disease among the different disorders that can lead to dementia[23]. In addition to these changes, cerebral glucose hypometabolism is observed decades before the onset of symptoms[24,25].

Glucose Hypometabolism

The human brain weighs about 2% to 3% of the weight of an adult and uses approximately 20% to 23% of the daily energy requirement[24]. Most of the glucose consumed is used to maintain the pre- and postsynaptic ion gradient necessary for glutamatergic neurotransmission[26]. Glucose transporters (GLUTs) are responsible for glucose uptake. GLUT1, located in the blood-brain barrier, and GLUT3, located in the neurons, are the main GLUTs in the brain. These transporters are not sensitive to insulin, and the glucose uptake process is correlated to its concentration on both sides of the blood-brain barrier (BBB)[27]. On the other hand, GLUT4 is insulin dependent, being present in different regions of the brain related to memory and cognition[28].

In the human brain affected by AD, glucose transport is reduced in most metabolically active brain regions, such as the cortex and hippocampus[29, 30]. Post-mortem brain analysis of AD patients showed decreased levels of GLUT1 and GLUT3 in the cerebral cortex[31], with significant loss of the neuronal glucose transporter GLUT3. These lower levels are associated with the most severe AD pathology[32], which decreases glucose uptake by neurons[33].

Furthermore, some studies have shown that cerebral insulin signaling may be impaired in AD patients[34,35] when compared to control subjects[36]. The Rotterdam study, published in 1996, demonstrated that patients with type 2 diabetes mellitus (DM2) had twice as much AD as healthy subjects[37]. Since then, there has been a growing number of studies associating DM2 to DA[38-45], with inflammation, insulin resistance, and mitochondrial dysfunction being common signs in both diseases[35].

Insulin resistance and, consequently, reduced glucose uptake and use, decrease neuronal cell energy, homeostatic functions, and synaptic connection[46]. Thus, a decreased glucose metabolism results in decreased cholinergic

transmission and nerve cell atrophy. This is because acetylcholine synthesis (ACh) is extremely sensitive to glucose metabolism in the brain, since it occurs exclusively in the glycolytic pathway, impairing synapses and, consequently, neurotransmission[47]. At the cellular level, AD is associated with reduced ACh in the synaptic process, decreasing cholinergic neurotransmission[48]. The low availability of glucose is also related to tau protein hyperphosphorylation[49,50] and unbalanced homeostatic functions, such as increased oxidative stress and mitochondrial dysfunction with the generation of reactive oxygen (ROS) and reactive nitrogen (RNS) species[51].

Brain glucose uptake and metabolism are assessed using the cerebral glucose metabolic rate (CGMR)[24]. Some studies indicate a 20% to 25% reduction in CGMR in AD, with earlier reductions in the hippocampal area (related to the processing of new information for long-term memory). CGMR reduction is also seen in areas related to space, sound and language interpretation and orientation, such as the parietal and temporal lobes[52,53]. In addition, there is a relationship between decreased CGMR and worsening cognitive status in AD patients[54].

As already discussed, the pathophysiology of AD is complex, and, so far, the treatment can delay disease progression, but cannot cure it. Thus, the search for other nonpharmacological measures has increased in recent years with the objective of contributing, at least partially, to slow the disease progression, especially if performed early. Based on the hypotheses that explain AD, it is possible to investigate nutritional mechanisms that can clinically benefit these patients.

• Alternative Energy Pathway

Although the brain's primary fuel is glucose, it is important to highlight that this organ can easily use ketone bodies during periods of prolonged fasting, which can be considered the main source of fuel in these situations[55-58]. Decreased plasma glucose and insulin levels, as occurs in periods of fasting or intense carbohydrate reduction, release free fatty acids that are beta-oxidized in the mitochondria. Excess acetyl-CoA increases ketone body production since there is extra acetyl-CoA to be used in the Krebs cycle[58].

The comparison between the cerebral metabolic rates of glucose (CMRG) and ketone bodies, such as the cerebral acetoacetate metabolic rate (CAMR), in patients with or without AD shows a decreased CGMR in the gray matter of mild AD patients, **while the CAMR presents no difference between groups**[59,60]. In addition, there is a linear relationship between the plasma concentration and brain uptake of ketone bodies in these patients[58,60], **suggesting that ketone bodies can compensate for the energy deficit in AD patients**[24,58] **and be a great strategy to improve cerebral energy metabolism**[61].

• Caprylic and Capric Acids

Caprylic (C8:0) and capric acids (C10:0) are medium-chain fatty acids recognized for their ability to form ketone bodies[58,62,63] **even when added to a regular meal.** This happens due to a rapid absorption by the portal system and beta-oxidation in the liver, generating excess acetyl-Coa, which leads to ketone body formation[58,64].

Acetoacetate is the first ketone body produced[65], followed by beta-hydroxybutyrate (BHB), considered the main ketone body[66]. Ketone bodies cross the blood-brain barrier[67], enter neurons and generate ATP by oxidative phosphorylation in the mitochondria[58].

BHB acetoacetate levels reach 0.010 to 0.015 mM in the postprandial period[68]. Supplementation with 12 grams of caprylic acid combined with eight grams of capric acid, twice a day, brought BHB levels to 0.6 mM[69], indicating that the consumption of caprylic and capric acids safely induces mild to moderate ketonemia without the need for prolonged fasting or consumption of high fat content, as in the classic ketogenic diet. In addition, caprylic and capric acids do not stimulate fat deposition[63].

In AD patients, when plasma BHB levels are around 0.1 mM, ketone bodies provide more than 5% of brain energy, providing about 10% to 15% when reaching 1 mM[58]. The daily supplementation of 30 grams of capric acid combined with caprylic acid, or just caprylic acid, in mild to moderate AD patients, **decreased the brain energy deficit by 23%** due to an increased supply of ketone bodies, without changing the use of cerebral glucose[61]. Another study reported that, in addition to the increased plasma concentration of ketone bodies, the ingestion of 20 grams of capric acid combined with caprylic acid resulted in **cognitive improvements assessed through memory tests in participants with mild to moderate AD**[70].

One dose of **Instanth® NEO** provides
20 g of caprylic acid and 15 g of capric acid.

• Phosphatidylserine

Synaptic dysfunction is an important factor that increases cognitive impairment in AD[71]. Neuropathological analyses of AD patients show a strong association between degrees of cognitive impairment and synaptic changes[72]. **One of the causes may be related to the composition and function of neuronal membranes.**

Post-mortem brain analyses of AD patients showed changes in the composition of neuronal membranes, such as decreased phospholipid content, when compared to control subjects of the same age, who presented changes mainly in the hippocampus and cerebral cortex[73,74,76-78].

Among phospholipids, decreased phosphatidylserine (PS) in neuronal membranes has been associated with

impaired memory and deficits in mental cognitive abilities[75], since PS plays a fundamental role in neuronal membrane functioning[76-78].

Oral supplementation of PS crosses the blood-brain barrier, increasing the supply of this compound to the brain[79], which is related to increased interneuronal communication due to an increased fluidity of cell membranes[80-82]. PS is also related to cholinomimetic action, inhibiting cholinesterase, an enzyme that degrades ACh, in addition to being related to glucose metabolism[76]. Probable AD subjects presented an increase of 15% in CGMR after three weeks of PS supplementation (500 mg/day)[83].

A randomized double-blind controlled study on patients diagnosed with probable AD, receiving supplementation of 200 mg of PS daily for three months, reported significant improvements in memory, information processing, and the ability to perform daily activities compared to the placebo group[84]. In another study, patients diagnosed with AD who received supplementation of 300 mg of PS daily for five months presented increased cognitive assessment scores in vocabulary and image memory tests after treatment[85].

One dose of **Instanth® NEO** provides 300 mg of PS and 459 mg of choline.

PS is a constituent of neuronal membranes that protects cell membranes against oxidative damage[86]. In AD patients, PS seems to inhibit the oxidation of cell membrane phospholipids caused by ROS[87]. **Choline is an important nutrient in the metabolism of phospholipids** that also plays a role in cholinergic dysfunction and in synaptic membrane functioning[88]. In AD, the need for choline increases due to the high brain levels necessary to correct synaptic dysfunction[89]. In this context, post-mortem research documented lower levels of choline and phospholipids in the brain of AD patients compared to controls of the same age[90]. In animal models, choline supplementation increased free choline and ACh concentrations in the cortex and hippocampus, indicating improved cognitive deficits and anxiety, and decreased ß-amyloid deposition[91].

• Docosahexaenoic acid (DHA)

Brain cell membranes are rich in Ω3 polyunsaturated fatty acids, such as DHA. However, in AD, DHA levels are decreased[92] and there is significant experimental evidence that DHA deficiency or enrichment in the hippocampus is associated, respectively, with decreased or increased learning related to memory skill[93].

In addition, about 20% to 30% of the PS content in the gray matter is combined with DHA[94.95]. A reduction in PS DHA content in the cerebral cortex is associated with the progression of mild cognitive impairment to AD[86,96]. Consequently, the incorporation of PS into human membranes depends on the availability of PS itself, but also of DHA[86,94]. DHA positively modulates PS biosynthesis and reserves in neuronal cells that promote survival and inhibit apoptosis, in a PS-dependent manner. In addition, the combined supplementation of DHA and PS significantly reduced nitric oxide (NO) levels (which demonstrated antioxidant activity), in the brain tissue of animals, being more efficient than the supplementation of DHA or PS alone[97].

A double-blind placebo-controlled trial investigating the safety of using 300 mg of PS combined with 79 mg of Ω3 for 15 weeks showed that this supplementation was safe and well tolerated[98]. Another double-blind placebo-controlled study showed that the same dose of PS combined with DHA improved cognitive performance in older patients with memory complaints[99].

One dose of **Instanth® NEO** provides 180 mg of DHA.

• Hyperhomocysteinemia and AD

High levels of homocysteine have been linked to coronary and brain diseases, such as AD[100-104]. Homocysteine acts on mechanisms involved in the etiology of AD, such as abnormal tau phosphorylation and β-amyloid peptide accumulation. Thus, homocysteine is considered a risk factor for AD[105], and, associated with B vitamins, has etiological importance in AD[106], since homocysteine is metabolized through two pathways dependent on vitamin B12, folic acid, and vitamin B6[107].

Vitamin B12 associated with folate plays a crucial role in the methionine synthetase reaction[108], an enzyme that promotes the methylation of homocysteine into methionine. Thus, folic acid and vitamin B12 supplementation is related to decreased homocysteine levels[109]. Low serum concentrations of vitamin B12 and folic acid, and, consequently, the low availability of methyl groups in the brain, also impair the formation of various membrane neurotransmitters and phospholipids[110].

In addition to being related to hyperhomocysteinemia, folate deficiency may be related to protein phosphatase 2A deficiency, leading to abnormal expression of hyperphosphorylated tau protein[111], which, as mentioned before, is one of the accepted hypotheses for the etiology of AD.

A randomized controlled clinical study using high doses of vitamin B12, B6 and folic acid was conducted to assess whether B vitamin supplementation could reduce the rate of cerebral atrophy in older patients with mild cognitive impairment. This study, known as VITACOG, demonstrated in brain magnetic resonance images that the group of patients receiving the vitamin complex had a significantly lower rate of global cerebral atrophy when compared to the placebo group. In addition, the study reported a relationship with basal homocysteine levels greater than 13 mmol/L and, in these cases, the rate of cerebral atrophy decreased by

53% with treatment[112]. Furthermore, there was a decrease in cerebral atrophy and cognitive decline in patients presenting good plasma levels of ω3[113] fatty acids, suggesting that the supplementation of B vitamins be combined with ω3 fatty acids[114].

One dose of **Instanth® NEO** provides 6.8 mcg of vitamin B12, 289 mcg of folic acid, and 20 mg of vitamin B6.

• Vitamin D

Vitamin D deficiency can impact the development of several diseases and accelerate aging[115], since this vitamin is related to neuronal protection[116]. Vitamin D receptors (VDR) are widely expressed throughout the central nervous system (CNS), with greater expression in the hippocampus, hypothalamus, thalamus, cortex, subcortex, and substantia nigra, essential areas for cognition[117].

Vitamin D has an anti-inflammatory action that can reverse age-related changes in the hippocampus in an animal model[118]. The neuroinflammation caused by ß-amyloid accumulation plays a key role in AD pathogenesis and progression[119], being represented by the increased expression of pro-inflammatory cytokines released by the non-neuronal cells astrocytes and microglia, auxiliary cells that support the SNC operation[120,121].

The probable neuroprotective mechanism of action of vitamin D occurs through the suppression of cerebral proinflammatory cytokines[122] and the recovery of the ability of macrophages to phagocyte ß-amyloid[123] - with its increased brain efflux - and, consequently, decrease the number of amyloid plaques[124,125].

In AD patients, hypovitaminosis D is associated with faster cognitive decline[126,127], which demonstrates the potential benefit of supplementing this nutrient.

One dose of **Instanth® NEO** provides 41 mcg of vitamin D.

• Mix of Antioxidant Vitamins and Minerals

Older people present decreased antioxidant levels in brain regions related to AD[128]. In AD, oxidative stress is closely related to mitochondrial dysfunction due to a defect in the electron transport chain and an increased production of free radicals[129], which increase neurodegeneration[130]. Thus, a combination of antioxidant vitamins and minerals must be present in the diet of AD patients.

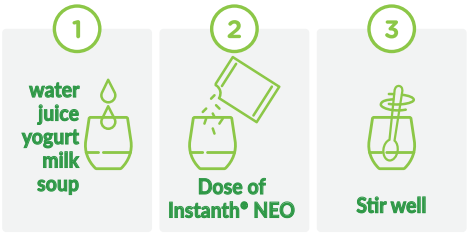
One dose of **Instanth® NEO** provides antioxidant vitamins and minerals: vitamins C and E, selenium, zinc, and magnesium.

• **Instanth® NEO** is a unique combination of nutrients for brain nutrition in Alzheimer's patients. Caprylic and capric acids increase ketone body formation, partially compensating for the energy deficit observed in AD patients. Phosphatidylserine plays a fundamental role in neuronal membrane functioning, supporting cognitive functions. However, the incorporation of phosphatidylserine in the membranes is mediated by DHA, which also supports the proper functioning of synapses. The combination of vitamins and minerals with anti-inflammatory and antioxidant properties present in **Instanth® NEO** supports the brain nutrition.

4-week adaptation (28 days): 2 boxes with 37 sachets (13.75 grams each).

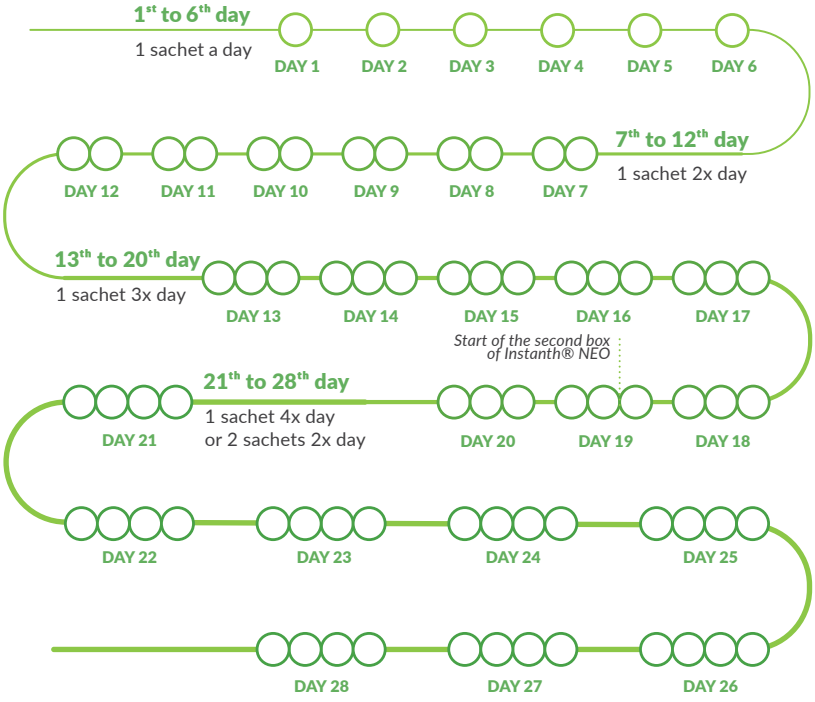
Adaptation period	Duration	Quantity	Number of sachets for the period
1st to 6th day	6 days	1 sachet 1x day	6 sachets
7th to 12th day	6 days	1 sachet 2x day	12 sachets
13th to 20th day	8 days	1 sachet 3x day	24 sachets
21st to 28th day	8 days	1 sachet 4x day or 2 sachets 2x day (2 to 4 days)	36 sachets

How to use:



During the adaptation period, **Instanth® NEO** should be consumed after meals.

Consumption guidance for the adaptation period



Continuous use after the adaptation period:

4 sachets of 13.75 g consumed preferably together, or 2 sachets of 13.75 g twice a day.

PRODIET J 2019; 1 (1):1-10
PRODIET MEDICAL NUTRITION

References:

1. Brayne C, et al. Dementia before death in ageing societies--the promise of prevention and the reality. PLoS Med; 3(10):e397. 2006.
2. Prince M, et al. The global prevalence of dementia: a systematic review and metaanalysis. Alzheimers Dement. Jan;9(1):63-75.e2. 2013.
3. World Health Organization. Global action plan on the public health response to dementia 2.017–2.025. Geneva: World Health Organization; 2017.
4. Alzheimer's Disease International. World Alzheimer Report 2018. The state of the art of dementia research: New frontiers. Alzheimer's Disease International (ADI), London. September 2018.
5. Burla, C et al. Panorama prospectivo das demências no Brasil: um enfoque demográfico. Ciênc. saúde coletiva, Rio de Janeiro , v. 18, n. 10, p. 2949-2956, Oct. 2013.
6. Alzheimer's Association. 2018 Alzheimer's Disease Facts and Figures. Alzheimers Dement;14(3):367-429. 2018.
7. Lehtovirta M, et al. Clinical and neuropsychological characteristics in familial and sporadic Alzheimer's disease: relation to apolipoprotein E polymorphism. Neurology. 46(2):413–9. 1996.
8. Smith MAC. Doença de Alzheimer. Rev Br Psiq. 21(s.2):3-7. 1999.
9. FROTA, Norberto Anízio Ferreira et al . Criteria for the diagnosis of Alzheimer's disease: Recommendations of the Scientific Department of Cognitive Neurology and Aging of the Brazilian Academy of Neurology. Dement. neuropsychol. São Paulo , v. 5, n. 3, p. 146-152, Sept. 2011.
10. McKhann, G.M, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement, 7, pp. 263-269. 2011.
11. Yang, IH et al . Aceite de coco: tratamiento alternativo no farmacológico frente a la enfermedad de Alzheimer. Nutr. Hosp., Madrid , v. 32, n. 6, p. 2822-2827, dic. 2015.
12. Albert, M.S, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement, 7 pp. 270-279, 2011.
13. Mitchell AJ, Shiri-Feshki M. Rate of progression of mild cognitive impairment to dementia—metaanalysis of 41 robust inception cohort studies. Acta Psychiatr Scand. 119:252–265. 2009.
14. Roberts R, Knopman DS. Classification and epidemiology of MCI. Clin Geriatr Med. November; 29(4). 2013.
15. Sperling, R.A, et al. Towards defining the preclinical stagse of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement, 7, pp. 280-292. 2011.
16. Hardy, J. A.; Higgins, G. A. Alzheimer's disease: the amyloid cascade hypothesis. Science, 256, 184. 1992.
17. Sheng M, Sabatini BL, Südhof TC. Synapses and Alzheimer's disease. Cold Spring Harb Perspect Biol. May 1;4(5). 2012.
18. Lacor PN et al. Synaptic targeting by Alzheimer's-related amyloid beta oligomers. J Neurosci. Nov 10;24(45):10191-200 2004.
19. Selkoe D, Mandelkow E, Holtzman D. Deciphering Alzheimer disease. Cold Spring Harb Perspect Med.2(1):a011460. 2012.
20. Selkoe DJ. Amyloid beta-protein and the genetics of Alzheimer's disease. J Biol Chem. Aug 2;271(31):18295-8. 1996.
21. MOHANDAS E, RAJMOHAN V, RAGHUNATH B. Neurobiology of Alzheimer's disease. Indian J Psychiatry. Jan;51(1):55-61. 2009.
22. Kanaan NM et al. Axonal degeneration in Alzheimer's disease: when signaling abnormalities meet the axonal transport system. Exp Neurol. Aug; 246:44-53. 2013.
23. Jack CR Jr et al. NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. Alzheimers Dement. Apr;14(4):535-562. 2018.
24. Cunnane, S. et al. Brain fuel metabolism, aging, and Alzheimer's disease. Nutrition 27, 3–20. 2011.
25. Bateman RJ. Clinical and Biomarker Changes in Dominantly Inherited Alzheimer's Disease. N Engl J Med 367;9 august 30, 2012.
26. Shulman RG, et al. Energetic basis of brain activity: implications for neuroimaging. Trends Neurosci. Aug;27(8):489-95. 2004.
27. Duelli R, Kuschinsky W. Brain glucose transporters: relationship to local energy demand. News Physiol Sci.16:71–6. 2001.
28. Watson, G.S.; Craft, S. Modulation of memory by insulin and glucose: Neuropsychological observations in alzheimer's disease. Eur. J. Pharmacol. 490, 97–113. 2004.
29. Jagust WJ, et al. Diminished glucose transport in Alzheimer's disease: dynamic PET studies. J Cereb Blood Flow Metab. Mar;11(2):323-30. 1991.
30. Piert M, et al. Diminished glucose transport and phosphorylation in alzheimer's disease determined by dynamic FDG-PET.J Nucl Med 37, 201-208. 1996.
31. Simpson IA, et al. Decreased concentrations of GLUT1 and GLUT3 glucose transporters in the brains of patients with Alzheimer's disease. Ann Neurol; 35:546–551. 1994.
32. An Y, et al. Evidence for brain glucose dysregulation in Alzheimer's disease. Alzheimers Dement;14(3):318–329. 2018.
33. Szablewski L. Glucose Transporters in Brain: In Health and in Alzheimer's Disease. J Alzheimers Dis. 55(4):1307-1320. 2017.
34. Cole GM, Frautschy SA. The role of insulin and neurotrophic factor signaling in brain aging and Alzheimer's Disease. Exp Gerontol; 42(1–2):10–21. 2007.
35. De Felice FG, Ferreira ST. Inflammation, defective insulin signaling, and Mitochondrial dysfunction as common molecular denominators connecting type 2 diabetes to Alzheimer disease. Diabetes. Jul;63(7):2262-72. 2014.
36. Freude S, Schilbach K, Schubert M. The role of IGF-1 receptor and insulin receptor signaling for the pathogenesis of Alzheimer's disease: from model organisms to human disease. Curr Alzheimer Res.. 6:213-223. 2009.
37. Ott A, et al. Association of diabetes mellitus and dementia: the Rotterdam Study. Diabetologia. Nov;39(11):1392-7. 1996.
38. Rivera EJ, Goldin A, Fulmer N, et al. Insulin and insulin-

like growth fator expression and function deteriorate with progression of Alzheimer's disease: link to brain reductions in acetylcholine. J Alzheimers Dis. 8:247-268. 2005.

39. Ronnemaa E, et al. Vascular risk factors and dementia: 40-year follow-up of a population-based cohort. Dement Geriatr Cogn Disord, 31:460–466. 2011.
40. Sims-Robinson C, et al. How does diabetes accelerate Alzheimer disease pathology? Nat Rev Neurol. 6:551–559. 2010.
41. Crane PK, Walker R, Larson EB. Glucose levels and risk of dementia. N Engl J Med. Nov 7;369(19):1863-4. 2013.
42. Ferreira ST, et al. Inflammation, defective insulin signaling, and neuronal dysfunction in Alzheimer's disease. Alzheimers Dement. Feb; 10 (1 Suppl):S76-83. 2014.
43. Verdile G, Fuller SJ, Martins RN. The role of type 2 diabetes in neurodegeneration. Neurobiol Dis. Dec;84:22-38. 2015.
44. Lourenco, M. V.; Ferreira, S. T.; De Felice, F. G. Neuronal stress signaling and eIF2α phosphorylation as molecular links between Alzheimer's disease and diabetes. Prog. Neurobiol. 129, 37. 2015.
45. Pal K, et al. Mild cognitive impairment and progression to dementia in people with diabetes, prediabetes and metabolic syndrome: a systematic review and meta-analysis. Soc Psychiatry Psychiatr Epidemiol. Nov; 53(11):1149-1160. 2018.
46. De la Monte S M and Tong M. Brain metabolic dysfunction at the core of Alzheimer's disease. Biochem Pharmacol;88:548-559. 2014.
47. Meier-Ruge W, Bertoni-Freddari C, Iwangoff P. Changes in brain glucose metabolism as a key to the pathogenesis of Alzheimer's disease. Gerontology. 40(5):246-52. 1994.
48. FORLENZA, OV. Tratamento farmacológico da doença de Alzheimer. Rev. psiquiatr. clín., São Paulo, v. 32, n. 3, p. 137-148, June 2005.
49. Liu F, et al. O-GlcNAcylation regulates phosphorylation of tau: a mechanism involved in Alzheimer's disease. Proc Natl Acad Sci USA; 101:10804–10809. 2004.
50. Liu Y, et al. Decreased glucose transporters correlate to abnormal hyperphosphorylation of tau in Alzheimer disease. FEBS Lett. January 23; 582(2): 359–364. 2008.
51. MATIOLI MN, NITRINI, R. Mechanisms linking brain insulin resistance to Alzheimer's disease. Dement. neuropsychol., São Paulo, Jun;9(2):96-102. 2015.
52. Mosconi L, et al. Maternal family history of Alzheimer's disease predisposes to reduced brain glucose metabolism. Proceedings of the National Academy of Sciences of the United States of America; 104(48):19067–72. 2007.
53. Silverman DH, et al. Positron emission tomography scans obtained for the evaluation of cognitive dysfunction. Seminars in nuclear medicine. 38(4):251–61. 2008.
54. Shoghi-Jadid K, et al. Localization of neurofibrillary tangles and beta-amyloid plaques in the brains of living patients with Alzheimer disease. Am J Geriatr Psychiatry. Jan-Feb;10(1):24-35. 2002.
55. Owen OE, et al. Brain Metabolism during Fasting. J Clin Invest. Oct; 46(10): 1589–1595. 1967.
56. Drenick, E.J. et al. Resistance to symptomatic insulin reactions after fasting. J. Clin. Invest. 51: 2757–2762. 1972.
57. Sokoloff L. Energetics of functional activation in neural tissues. Neurochem Res.; 24(2):321–9. 1999.
58. Cunnane SC, et al. Can Ketones Help Rescue Brain Fuel Supply in Later Life? Implications for Cognitive Health during Aging and the Treatment of Alzheimer's Disease. Front. Mol. Neurosci. Jul. 2016.
59. Lying-Tunell, U. et al. Cerebral blood flow and metabolic rate of oxygen, glucose, lactate, pyruvate, ketone bodies and amino acids. Acta Neurol. Scand. 63: 337–350. 1981.
60. Castellano CA, et al. Lower brain 18F-fluorodeoxyglucose uptake but normal 11C-acetoacetate metabolism in mild Alzheimer's disease dementia. J Alzheimers Dis;43(4):1343-53. 2015.
61. Croteau E, et al. Ketogenic Medium Chain Triglycerides Increase Brain Energy Metabolism in Alzheimer's Disease. J Alzheimers Dis. 64(2):551-561. 2018.
62. Seaton, T.B. et al. Thermic effect of medium-chain and long-chain triglycerides in man. Am. J. Clin. Nutr. 44: 630–634. 1986.
63. Courchesne-Loyer A. Stimulation of mild, sustained ketonemia by medium-chain triacylglycerols in healthy humans: estimated potential contribution to brain energy metabolism. Nutrition. Apr;29(4):635-40. 2013.
64. Schönfeld P, Wojtczak L. Short- and medium-chain fatty acids in energy metabolism: the cellular perspective. J Lipid Res. Jun;57(6):943-54. 2016
65. Puisac, B., et al. Characterization of splice variants of the genes encoding human mitochondrial HMG-CoA lyase and HMG-CoA synthase, the main enzymes of the ketogenesis pathway. Mol Biol Rep. 39, 4777-4785. 2012.
66. Kalapos, M.P. On the mammalian acetone metabolism: from chemistry to clinical implications. Biochimica et Biophysica Acta (BBA) - General Subjects 1621, 122-139. 2003.
67. Simpson, I.A., Carruthers, A., Vannucci, S.J. Supply and demand in cerebral energy metabolism: the role of nutriente transporters. J. Cereb.Blood Flow Metab. 27, 1766–1791. 2007.
68. Veech RL. Ketone bodies, potential therapeutic uses. IUBMB Life. Apr;51(4):241-7. 2001.
69. Vandenberghe C. Tricaprylin Alone Increases Plasma Ketone Response More Than Coconut Oil or Other Medium-Chain Triglycerides: An Acute Crossover Study in Healthy Adults. Curr Dev Nutr. Apr; 1(4): e000257. 2017.
70. Ota M, et al. Effects of a medium-chain triglyceride-based ketogenic formula on cognitive function in patients with mild-to-moderate Alzheimer's disease. Neurosci Lett. Jan 18;690:232-236. 2019.
71. Selkoe DJ. Alzheimer's disease is a synaptic failure. Science. Oct 25;298(5594):789-91. 2002.
72. Mucke L, Selkoe DJ. Neurotoxicity of amyloid ß-protein: synaptic and network dysfunction. Cold Spring Harb Perspect Med. Jul;2(7):a006338. 2012.
73. Chan RB, et al. Comparative lipidomic analysis of mouse and human brain with Alzheimer disease. J Biol Chem; 287(4):2678–88. 2012.
74. Martín V. Lipid alterations in lipid rafts from Alzheimer's disease human brain cortex. J Alzheimers Dis.19(2):489-502. 2010.
75. Oma S, et al. Changes in phospholipid composition of erythrocyte membrane in Alzheimer's disease. Dement Geriatr Cogn Disord Extra. 2:298–303. 2012.

76. Bruni A. Pharmacological effects of phosphatidylserine liposomes. Nature. volume 260, pages 331–333. 1976.

77. Samson JC: The biological basis of phosphatidylserine pharmacology. Clin Trials J. 24:1-8. 1987.

78. Vance, JE, Steenbergen R. Metabolism and functions of phosphatidylserine, Prog. Lipid Res. 44, 207–234. 2005.

79. Rosadini G., et al. Phosphatidylserine: quantitative EEG effects in healthy volunteers. Neuropsychobiology 24: 42-48, 1991.

80. Cenacchi T. Cognitive decline in the elderly: a double-blind, placebo-controlled multicenter study on efficacy of phosphatidylserine administration. Aging (Milano). Apr;5(2):123-33. 1993.

81. Cohen, AS; Müller WE. Age-Related alterations of NMDA-receptor properties in the mouse forebrain: partial restoration by chronic phosphatidylserine treatment. Brain Research, 584, 174-180. 1992.

82. Crook, TH. Effects of phosphatidylserine in age-associated memory impairment. Neurol. 41, 644-649. 1991.

83. Klinkhammer P, Szelies B, Heiss W.D. Effect of Phosphatidylserine on Cerebral Glucose Metabolism in Alzheimer's Disease. Dement Geriatr Cogn Disord; 1:197–201. 1990.

84. Amaducci, ML. et al. Phosphatidylserinc in the treatment of Alzheimer's disease. Results of a Multicentric Study. Psychopharmacol. Bull. 24, 130 134. 1988.

85. Zhang Y.Y., Yang L.Q., Guo L.M. Effect of phosphatidylserine on memory in patients and rats with Alzheimer's disease. Genet Mol Res. Aug 10;14(3):9325-33. 2015.

86. Glade MJ, Smith K. Phosphatidylserine and the human brain. Nutrition. Jun;31(6):781-6. 2015.

87. Amaducci L et al. Use of phosphatidylserine in Alzheimer's disease. Ann N Y Acad Sci. 640:245-249. 1991.

88. Tayebati SK, Amenta F. Choline-containing phospholipids: relevance to brain functional pathways. Clin Chem Lab Med. Mar 1;51(3):513-21. 2013.

89. Wang WY, et al. Role of pro-inflammatory cytokines released from microglia in Alzheimer's disease. Ann Transl Med. Jun; 3(10): 136. 2015.

90. Nitsch RM, et al. Evidence for a membrane defect in Alzheimer disease brain. Proc Natl Acad Sci U S A. Mar 1;89(5):1671-5. 1992.

91. Wang, Y, et al. Choline Supplementation Ameliorates Behavioral Deficits and Alzheimer's Disease-Like Pathology in Transgenic APP/PS1 Mice. Mol Nutr Food Res. Jul 12:e1801407. 2019.

92. Plourde, M, et al. Plasma incorporation, apparent retroconversion and betaoxidation of 13C-docosahexaenoic acid in the elderly. Nutr. Metab. (Lond) 8, 5. 2011.

93. Belkouch M, et al. The pleiotropic effects of omega-3 docosahexaenoic acid on the hallmarks of Alzheimer's disease. J Nutr Biochem. 38:1–11. 2016.

94. Kimura AK, Kim HY. Phosphatidylserine synthase 2: high efficiency for synthesizing phosphatidylserine containing docosahexaenoic acid. J Lipid Res; 54:214–22. 2013.

95. Tanaka K, et al. Effects of Docosahexaenoic Acid on Neurotransmission. Biomol Ther (Seoul). Mar; 20(2): 152–157. 2012.

96. Cunnane SC, et al. Plasma and brain fatty acid profiles in mild cognitive impairment and Alzheimer's disease. J Alzheimers Dis; 29:691–7. 2012.

97. Liu SH, et al. Docosahexaenoic acid and phosphatidylserine supplementations improve antioxidant activities and cognitive functions of the developing brain on pentylenetetrazol-induced seizure model. Brain Res. Apr 27; 1451:19-26. 2012.

98. Vakhapova V, et al. Safety of phosphatidylserine containing omega-3 fatty acids in non-demented elderly: a double-blind placebo-controlled trial followed by an open-label extension. BMC Neurol. Jun 28;11:79. 2011.

99. Vakhapova V et al. Phosphatidylserine containing omega-3 fatty acids may improve memory abilities in non-demented elderly with memory complaints: a double-blind placebo-controlled trial. Dement Geriatr Cogn Disord. 29(5):467-74. 2010.

100. Seshadri S, et al. Plasma homocysteine as a risk factor for dementia and Alzheimer's disease. N Engl J Med. Feb 14;346(7):476-83. 2002.

101. Ravaglia G et al. Homocysteine and cognitive function in healthy elderly Community dwellers in Italy. Am J Clin Nutr; 77:668–73. 2003.

102. Ravaglia G et al. Homocysteine and folate as risk factors for dementia and Alzheimer disease. Am J Clin Nutr. Sep;82(3):636-43. 2005.

103. Beydoun MA. Epidemiologic studies of modifiable factors associated with cognition and dementia: systematic review and meta-analysis. BMC Public Health. Jun 24;14:643. 2014.

104. Farina N. Vitamin E for Alzheimer's dementia and mild cognitive impairment. Cochrane Database Syst Rev. Apr 18;4:CD002854. 2017.

105. Sachdev PS. Homocysteine and brain atrophy. Prog Neuropsychopharmacol Biol Psychiatry. Sep;29(7):1152-61. 2005.

106. Robinson N, Grabowski P, Rehman I. Alzheimer's disease pathogenesis: Is there a role for folate? Mech Ageing Dev. Sep;174:86-94. 2018.

107. McLean RR, Hannan MT. B vitamins, homocysteine, and bone disease: epidemiology and pathophysiology. Curr Osteoporos Rep. Sep;5(3):112-9. 2007.

108. Mooijaart SP et al. Homocysteine, vitamin B-12, and folic acid and the risk of cognitive decline in old age: the Leiden 85-Plus study. Am J Clin Nutr. Oct;82(4):866-71. 2005.

109. Homocysteine Lowering Trialists' Collaboration. Lowering blood homocysteine with folic acid based supplements: meta-analysis of randomised trials. Homocysteine Lowering Trialists' Collaboration. BMJ. Mar 21;316(7135):894-8. 1998.

110. Hutto, B.R. Folate and cobalamin in psychiatric illness. Compr. Psychiatry, 38, 305–314. 1997.

111. Li W et al. Folic acid inhibits tau phosphorylation through regulation of PP2A methylation in SH-SY5Y cells. J Nutr Health Aging. Feb;19(2):123-9. 2015.

112. Smith AD, et al. Homocysteine-lowering by B vitamins slows the rate of accelerated brain atrophy in mild cognitive impairment: a randomized controlled trial. PLoS One. Sep 8;5(9):e12244. 2010.

113. Jernerén F, et al. Brain atrophy in cognitively impaired elderly: the importance of long-chain x-3 fatty acids and B vitamin status in a randomized controlled trial. Am J Clin Nutr; 102:215–21. 2015.

114. Szczechowiak K, Diniz BS, Leszek J. Diet and Alzheimer's dementia - Nutritional approach to modulate inflammation. Pharmacol Biochem Behav. Sep;184:172743. 2019.

115. Keisala T. Premature aging in vitamin D receptor mutant mice. J Steroid Biochem Mol Biol. Jul;115(3-5):91-7. 2009.

116. Buell JS, Dawson-Hughes B. Vitamin D and neurocognitive dysfunction: preventing "D"ecline? Mol Aspects Med. Dec; 29(6): 415-22. 2008.

117. Banerjee A, et al. Vitamin D and Alzheimer's Disease: Neurocognition to Therapeutics. Int J Alzheimers Dis.192747. 2015.

118. Moore ME, et al. Evidence that vitamin D3 reverses age-related inflammatory changes in the rat hippocampus. Biochem Soc Trans; 33:573-7. 2005.

119. Sastre M, Klockgether T, Heneka MT. Contribution of inflammatory processes to Alzheimer's disease: molecular mechanisms. Int J Dev Neurosci. Apr-May; 24(2-3):167-76. 2006.

120. Fuster-Matanzo A. Role of neuroinflammation in adult neurogenesis and Alzheimer disease: therapeutic approaches. Mediators Inflamm. 260925. 2013.

121. Serrano-Pozo A, et al. Neuropathological alterations in Alzheimer disease. Cold Spring Harb. Perspect. Med. 1, a006189. 2011.

122. Van Etten E, Mathieu, C. "Immunoregulation by 1,25-dihydroxyvitamin D3: basic concepts," The Journal of Steroid Biochemistry and Molecular Biology, vol. 97, no. 1-2, pp. 93–101, 2005.

123. Masoumi A, et al. 1alpha,25-dihydroxyvitamin D3 interacts with curcuminoids to stimulate amyloid-beta clearance by macrophages of Alzheimer's disease patients. J Alzheimers Dis. 17(3):703–717. 2009.

124. Ito, S. et al. "1α,25-Dihydroxyvitamin D3 enhances cerebral clearance of human amyloid-ß peptide(1–40) frommouse brain across the blood-brain barrier," Fluids and Barriers of the CNS, 8(8):20. 2011.

125. Yu, JM. et al. "Vitamin D3-enriched diet correlates with a decrease of amyloid plaques in the brain of AßPP transgenic mice," Journal of Alzheimer's Disease, 25(2):295-307. 2011.

126. Annweiler C, et al. Vitamine D et cognition chez la personne âgée: consensus et recommandations d'un groupe d'experts internationaux* Geriatr Psychol Neuropsychiatr Vieil; 14 (3): 265-73. 2016.

127. Lemire P. Cognitive changes under memantine according to vitamin D status in Alzheimer patients: An exposed/unexposed cohort pilot study. J Steroid Biochem Mol Biol. Jan;175:151-156. 2018.

128. Craft NE. Carotenoid, tocopherol, and retinol concentrations in elderly human brain. J Nutr Health Aging. 8(3):156-62. 2004.

129. Padurariu M, et al. The oxidative stress hypothesis in Alzheimer's disease. Psychiatria Danubina.25(4):401-9. 2013.

130. Fuller S, Steele M, Münch G. Activated astroglia during chronic inflammation in Alzheimer's disease--do they neglect their neurosupportive roles? Mutat Res. Aug 7;690(1-2):40-9. 2010.

PRODIET
MEDICAL NUTRITION

prodietnutrition.com

export@prodietnutrition.com